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C. LOVATT EVANS,

STUDIES IN EXPERIMENTAL TRAUMATIC SHOCK

IV. EVIDENCE OF A TOXIC FACTOR IN WOUND SHOCK

W. B. CANNON, M.D.
BOSTON

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Studies in Experimental Traumatic Shock

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During the last four years, clinical observations and laboratory studies have added materially to our knowledge of wound shock. Summarizing old and new features of this condition it may be said that it is characterized by a low venous pressure,¹ a low or falling arterial pressure, a rapid thready pulse, a diminished blood volume,² a normal or increased erythrocyte count and hemoglobin percentage in peripheral blood,³ a leukocytosis,⁴ an increased blood nitrogen,⁵ a reduced blood alkali,⁶ a lowered metabolism,⁷ a subnormal temperature, a cold skin, moist with sweat, a pallid or grayish or slightly cyanotic appearance, by thirst, by rapid respiration, often by vomiting and restlessness, and by anxiety, changing to mental dulness and lessened sensitivity. Many of these features may appear at once or as soon after the reception of the wound as the observations can be made; or they may develop only after the lapse of several hours.

INITIATING FACTORS IN SHOCK

The onset of early or *primary* shock is most reasonably accounted for as a consequence of some disturbance of the nervous system. A review of the evidence at hand shows that it is impossible to eliminate

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* Previous articles in this series are: Aub, J. C.: I. The Basal Metabolism, *Am. J. Physiol.* **54**:388 (Dec.) 1920. Aub, J. C., and Cunningham, T. D.: II. The Oxygen Content of the Blood, *Ibid.* **54**:408 (Dec.) 1920. Aub, J. C., and Wu, H.: III. Chemical Changes in the Blood, *Ibid.* **54**:416 (Dec.) 1920.

1. Wiggers, C. J.: *Am. J. Physiol.* **46**:326 (June) 1918. Erlanger, J.; Gesell, R., and Gasser, H. S.: *Ibid.* **49**:106 (June) 1919.

2. Keith: Blood Volume in Wound Shock, English Medical Research Committee, Report Series No. 26, March 14, 1919, p. 36. Gasser, H. S.; Erlanger, J., and Meek, W. J.: *Am. J. Physiol.* **50**:31 (Oct.) 1919.

3. Cannon, W. B.; Fraser, John, and Hooper, A. N.: Some Alterations in Distribution and Character of Blood in Shock and Hemorrhage, *J. A. M. A.* **70**:527 (Feb. 23) 1918.

4. Govaerts: *Ambulance de l'Océan* **2**:359, 1917. Keith: Blood Volume in Wound Shock, p. 8.

5. Duval and Grigaut: *Compt. rend. Soc. de biol.* **71**:873, 1918. Aub, J. C., and Wu, H.: *Am. J. Physiol.* **54**:416 (Dec.) 1920.

6. Cannon, W. B.: Acidosis in Cases of Shock, Hemorrhage and Gas Infection, *J. A. M. A.* **70**:531 (Feb. 23) 1918.

7. Aub, J. C.: *Am. J. Physiol.* **54**:388 (Dec.) 1920.

as a consequence of wounds a reflex relaxation of blood vessels similar to that which occurs in fainting. Indeed, as Cowell⁸ has observed, fainting is, in fact, not infrequently observed after the reception of wounds. Vincent⁹ likewise has seen cases of this character; but in the only instance which he describes in detail (that of a man wounded in the abdomen, who, a few minutes after being hit, manifested the syndrome of shock), the blood pressure, at the end of forty-five minutes, had risen from 60 to 90 millimeters of mercury. It is possible, then, that there may be produced by a wound an effect similar in character to fainting or syncope, but persisting for a longer period than the usual fainting spell.

British, French and American observers had occasion during the war to note that shock may begin to appear two or three hours after the wounding. It may be associated with continued bleeding, but commonly cannot be explained by hemorrhage or infection. Exposure to cold, lack of water, rough transportation, and the agitation of broken bones have been recognized as circumstances favorable to its development. These factors may later have their action increased by infection, especially by the bacilli of gas gangrene. This is *secondary* wound shock and was by far the most common form noted during the war. An analysis of the theories which have been most commonly advocated in the past, such as inhibition,¹⁰ reduction of the carbon dioxid content of the blood (acapnia¹¹), fat embolism,¹² exhaustion of nerve centers and of certain glands,¹³ shows that they do not offer an adequate explanation for the onset of delayed or secondary shock. Their chief and common defect is that they fail to account for the occurrence, both in clinical and in experimental shock, of a diminution of blood volume and either a local or a general concentration of blood corpuscles. A group of theories which do take these facts into consideration, namely, those which postulate a primary vasoconstriction with a consequent capillary congestion,¹⁴ fail in that they do not suggest how a vasoconstriction would occur, capable of bringing about a reduction of blood volume. What is required is a demonstra-

8. Cowell, E. M.: The Initiation of Wound Shock, J. A. M. A. **70**:608 (March 2) 1918.

9. Vincent: Compt. rend. Soc. de biol. **81**:887, 1918.

10. Meltzer, S. J.: The Nature of Shock, Arch. Int. Med. **1**:578 (July 15) 1908.

11. Henderson: Am. J. Physiol. **21**:128, 1908.

12. Porter: Harvey Lectures, Philadelphia, 1917-1919, p. 21.

13. Crile, G. W., and Lower, W. E.: Surgical Shock and the Shockless Operation Through Anoci-Association, Philadelphia, W. B. Saunders Company, 1920.

14. Malcolm: Tr. Med. Soc., London **32**:274, 1909. Starling, E. H.: Arch. méd. belges **71**:369 (Oct.) 1918. Erlanger, J.; Gessell, R., et al.: Am. J. Physiol. **49**:90, 151, 345, 1919; Ibid. **50**:31, 104, 119, 1919.

tion of some factor, naturally related to the production of shock, which may so operate in the body that, when hemorrhage and infection are ruled out, the persistent low blood pressure characteristic of shock will become gradually established.

CHARACTER OF INJURIES ASSOCIATED WITH WOUND SHOCK

A primary consideration in experimental study of natural phenomena is that the phenomena reproduced under controllable conditions shall resemble as closely as possible those occurring in nature. This is a consideration which seems to have been largely neglected in experimental investigations of shock. No doubt, persistent low blood pressure can be produced by a variety of means. In support of various theories of shock, investigators have been able to duplicate certain aspects of the condition by protracted stimulation of nerves, by severe and long-continued manipulation of exposed intestines, by vigorous over-ventilation of the lungs, by repeated pushes against the stomach, by interrupting the circulation in large areas of the body, or by injecting into the blood stream relatively large amounts of oil or cream. Although such procedures cause changes similar to those which occur in natural shock, they do not reproduce the circumstances which occasion shock after ordinary wounds or injuries. Obviously, it is desirable to duplicate, so far as possible, the actual conditions which give rise to a shocklike state, and then to analyze them in order to determine what factor, or factors, among them is operative.

The typical nature of the wounds seen in cases of secondary shock may be judged from the following records made by a group working at Béthune.¹⁵ In reading these records, it should be understood that the wounds are often made by large ragged pieces of shell moving at high velocity. When such a missile breaks the femur or the ilium, for example, it smashes and tears extensively the overlying muscles, which, in the thigh and hip, form a thick layer. In all these cases, shock was present:

CASE 1.—E. G., compound fracture of left ulna and radius, arm nearly severed, wounds of right arm and left side, abdomen opened, intestine and omentum protruding.

CASE 2.—C. P. H., shell wounds of right thigh with fracture of the femur, and shell wounds of left arm with fracture of the humerus, wounds of the face.

CASE 3.—G. D., wounds of the left arm with fracture, left leg with fracture, flesh wounds of the right thigh and abdomen.

CASE 4.—G. J. H. H., shell wounds of right ankle, of left leg with fracture, and of the muscles of the buttock.

15. Cannon, W. B.: Acidosis in Cases of Shock, English Medical Research Committee, Report Series No. 25, Dec. 25, 1917, pp. 86-88.

CASE 5.—H. J. H., bursting shell broke right femur, left tibia and fibula, and injured right arm.

CASE 6.—A. J. R., extensive wounds of both legs, left foot and left arm.

CASE 7.—W. G., wounds of buttock with fracture of ilium, also wounds of right foot.

CASE 8.—P. K., fracture of left femur (much comminuted) and right tibia.

CASE 9.—W. A. T., wounds of buttock and perineum, muscles below the buttock torn across and smashed in both legs.

CASE 10.—G. K., wounds of both arms, left thigh, left foot, compound fracture of the right thigh.

CASE 11.—R. C., compound fracture of right femur, multiple shell wounds, left femur, buttock and chest.

CASE 12.—A. H., multiple shell wounds; large wound of the left loin involving the gluteal muscles, fracture of the pelvis, extensive wound of right calf muscles and the muscles of the left thigh and left calf, and numerous wounds in back and chest.

The general character of war wounds is well described by Wallace and Fraser:¹⁶

The tissues of the wound are crushed and lacerated, and there are widespread contusion and effusion of blood into the surrounding parts. The neighboring blood vessels are often pulped and thrombosed, and as a result of the interference with the blood supply whole areas of tissue may afterward die and slough away. In these wounds, muscle appears to be affected more than any other tissue; it becomes a mass of dark brown crushed matter without any evidence of striation or vitality. One cannot fail to be impressed by the enormous destruction which even a small fragment of shell will produce, a degree of destruction which is apparently quite out of keeping with the size of the fragment; the exaggerated damage depends on the enormous velocity at which the fragments are traveling.

EXPERIMENTAL EVIDENCE OF A TOXIC ORIGIN OF SECONDARY WOUND SHOCK

After spending the summer of 1917 at a casualty clearing station in Béthune, I went to London and worked for three months with Bayliss in an experimental study of shock. At first, we were interested in the question as to whether the acid known to be developed in injured tissue might not be a contributory factor in the production of shock as seen in man. The traumatization which we caused induced both a reduction of blood alkali (an acidosis) and a low blood pressure (Fig. 1). Later it was shown that the acid production was not an essential factor in the complex.¹⁷ Some other agent, therefore, must be acting. Further analysis of the mode of operation of the trauma will be deferred until the observed facts are described. These facts were estab-

16. Wallace and Fraser: *Surgery at a Casualty Clearing Station*, London, 1918, p. 31.

17. *Acidosis and Shock*, English Medical Research Committee, Report Series No. 25, October, 1919, p. 250.

lished in part by Bayliss and myself working together,¹⁸ and in part by each of us working independently, after I was transferred to the Laboratory of Surgical Research of the American Expeditionary Forces at Dijon, France.

In order to bring about, in lower animals, a traumatization similar to that giving rise to shock in man, the thigh muscles in the anesthetized cat, while being supported by an iron block, were repeatedly struck with a blunt wedge-shaped hammer, or they were crushed by compression. The trauma usually failed to break the skin, so that infection from without was impossible. Occasionally, the femur was broken, but this had no influence on the results which were seen. After this procedure, the course of events was followed in observations on the pulse, respiration and the alkali reserve and the corpuscular volume of the blood. In Figure 1 is presented a summary of the changes seen in a typical case. An actual record of the blood pressure changes of shock produced in this way is shown in Figure 2.

As Figure 2 proves, the crushing of the muscles in one hind leg of the cat may have no immediate effect. There may be a momentary rise or fall of arterial pressure. After about twenty minutes, however (and still longer in the dog), the pressure begins to fall. And after about an hour, the pressure has usually fallen to 80 millimeters of mercury, or even lower, i. e., to a shock level. There it may persist for several hours. In other words, the general bodily condition resembling shock is produced by duplicating the circumstances which induce shock in man. The only noteworthy difference is the presence of anesthesia (urethane). That this is not a determining factor is shown by the use of a controllable anesthetic, such as ether, which may be lightened as the animal falls into deeper and deeper insensibility. The lessening of the ether concentration under these circumstances does not improve the circulation.

The fall of pressure after traumatization might be regarded as due to loss of blood and lymph into the damaged tissues, for there is always considerable swelling of the injured region. This suggestion was tested, however, by removing *postmortem*, with symmetrical cuts, the two hind legs, one normal, the other injured, and weighing them. The difference of weight which, in some instances, was only 10 per cent.

18. For early reports of these observations, see: Cannon, W. B.: Med. Bull. Med. Research Soc., Am. Red Cross, Paris, April, 1918, p. 426; Compt. rend. Soc. de biol. **81**:850, 1918. Bayliss, W. M.: Intravenous Injection in Wound Shock, New York, Longmans, Green & Co., 1918. Cannon, W. B., and Bayliss, W. M.: Note on Muscle Injury in Relation to Shock, Report of a Special Committee on Surgical Shock, English Medical Research Committee, March 14, 1919, p. 19. Bayliss, W. M.: Further Observations on the Results of Muscle Injury and Their Treatment, *Ibid.*, p. 23. Cannon, W. B.: Some Characteristics of Shock Induced by Tissue Injury, *Ibid.*, p. 27; Mil. Surgeon **44**:494 (May) 1919.

of the estimated blood volume, would not represent enough extravasated blood to account for the fall of pressure. It must be admitted, of course, that loss of blood by extravasation, even when slight, may play a rôle in the subsequent development of the low pressure.

The widespread effect in the organism induced by the trauma might be due to nervous impulses. Such impulses on passing to the central

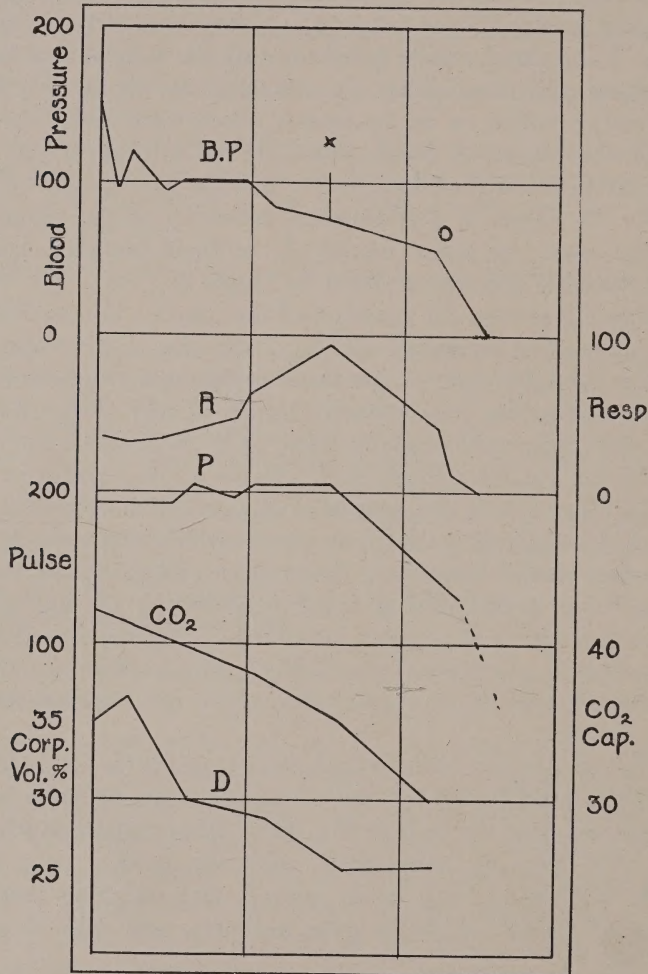


Fig. 1.—Record of changes in the blood pressure, respiration, pulse and carbon dioxid capacity (alkali reserve) of the plasma after injury of the flexor muscles in the thigh; urethane anesthesia. At X, asphyxia caused the rise of blood pressure indicated; at O, no rise in asphyxia.

nervous system might so affect it as to produce reflex inhibition of the vasoconstrictor center, as has been suggested above for the initiation of primary wound shock. Is such the case? The nature of the experiment permits securing evidence on this point. It is only necessary to

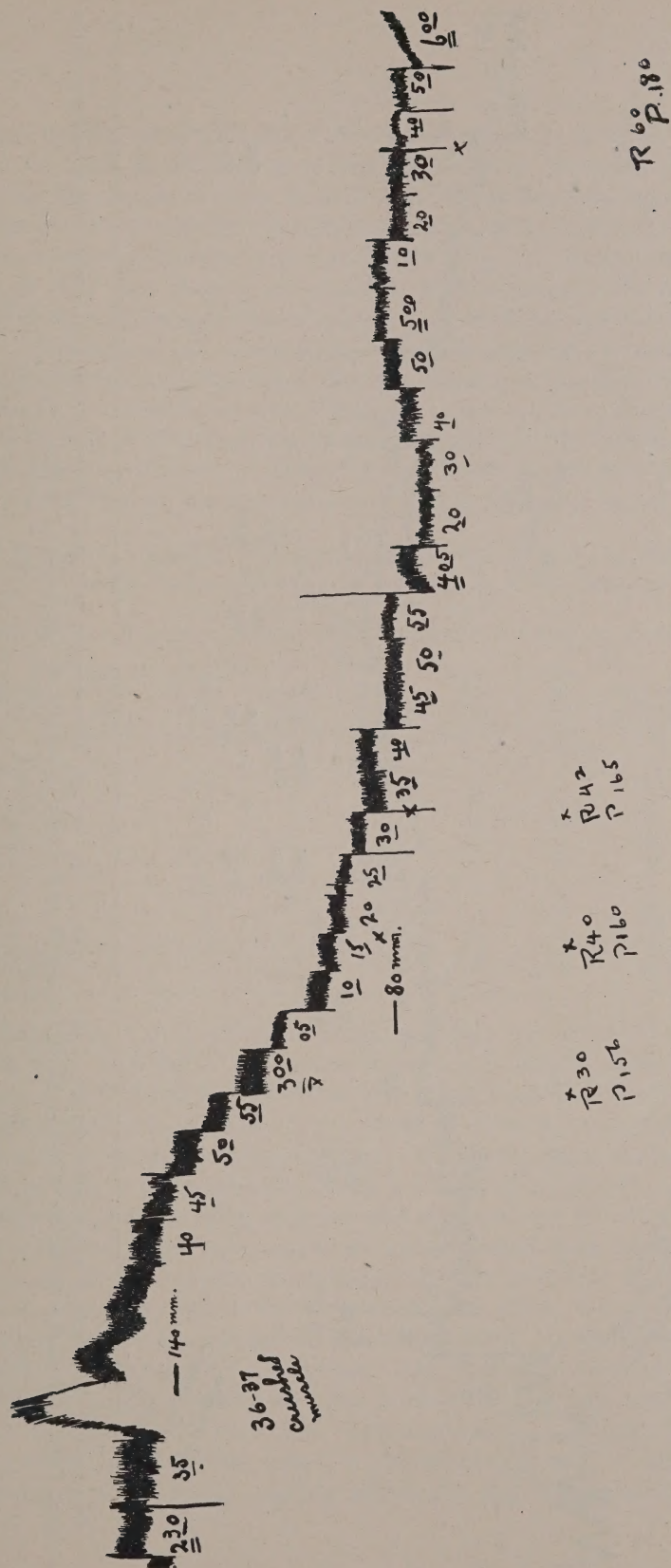


Fig. 2.—Typical fall of arterial blood pressure after crushing muscles of the thigh (at 2:36-2:37) : R, respiration ; P, pulse.

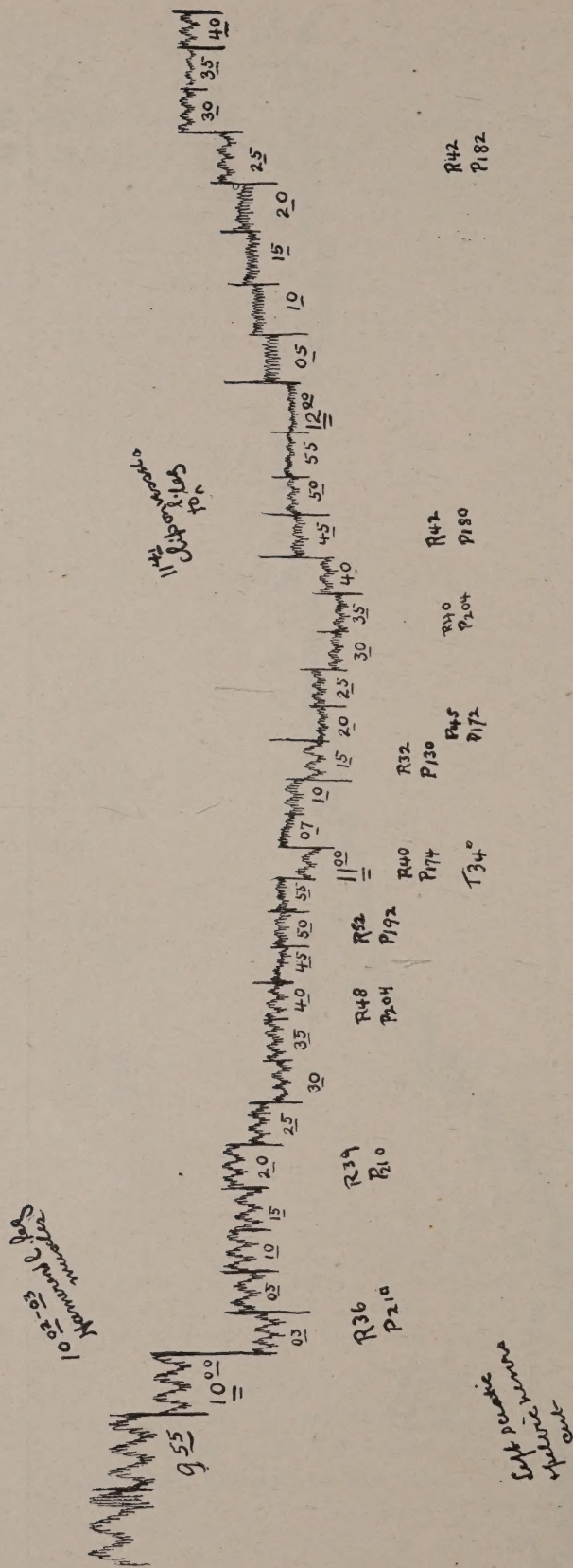


Fig. 3.—Fall of blood pressure after muscle injury (10:02-10:03), though the nerves to the injured limb had been cut; rise of blood pressure to the original level after closing (at 11:41) the blood vessels to and from the injured region: R, respiration; P, pulse.

transect the spinal cord above the lumbar plexus or to sever all nerves of the limb which is to be injured, in order to disconnect the region from the central nervous system. When this has been done and the denervated muscles are traumatized, events occur similar to those seen after trauma when the nerves are intact (Fig. 3). From this evidence it is clear that there is no essential relation between the production of shock and an excessive stimulation of the central nervous system.

The gradual fall of blood pressure, again, might be interpreted as due to depression or exhaustion of the central nervous system, with gradual loss of vasoconstrictor tone. That this is not true was shown by tests performed by Cattell in the Harvard laboratory. He used the method described by Bartlett, in which the rate of inflow of a fluid at constant pressure through the femoral artery of one hind limb was determined

SUMMARY OF RESULTS SHOWING PERFUSION TIME FOR 1 C.C. OF PHYSIOLOGIC SODIUM CHLORID SOLUTION IN RELATION TO BLOOD PRESSURE IN MUSCLE INJURY SHOCK

Experiment	Control Perfusion Time, Seconds	Maximal Perfusion Time, Seconds	Period After Injury, Hours	Percentage Increase	Perfusion Time at End, Seconds	Perfusion Time After Death, Seconds	Original Blood Pressure, Mm.	Blood Pressure at Maximal Constriction, Mm.
8	5.2	12.9	0.75	144	4.7	...	140	90
9	2.3	3.3	1.0	43	2.9	1.8	150	16
10	1.4	2.4	4.0	71	...	1.2	140	74
12	1.2	2.7	4.5	125	1.1	0.8	130	68
14	0.8	1.5	1.5	87	1.0	0.5	130	60
15	1.3	3.7	1.25	185	...	1.3	120	72
16	1.6	4.0	3.5	150	...	...	135	78
18	2.7	4.0	4.5	48	...	...	125	65
19	1.5	2.5	6.0	66	...	1.1	135	42
20	1.4	2.5	...	78	...	...	130	92
21	1.0	1.7	3.0	70	0.9	0.6	130	60
Average	1.85	3.74	3.0	102	2.1	1.0	131	65

at intervals during the development of shock produced by injury of the other hind limb. The inflow cannula was always placed in a side branch of the femoral artery, so that when injections were not being made, a clip on the main trunk could be removed to permit the leg to receive its natural blood supply. In Cattell's tests, about 3 c.c. of physiologic sodium chlorid solution was allowed to run into the artery while the time was being recorded with a stop watch. In a few instances in which perfusion was interfered with by small clots forming in the vessels, the experiments were discarded. The condition of the vessels was checked by inflow determinations after death, when, if there is no obstruction, the rate will be greatly increased. In the accompanying table is a summary of the results. The figures represent the time in seconds for the entrance of 1 c.c. of fluid, and in each case they are the average for at least three determinations. Invariably, there was a gradual increase in the time (i.e., decrease in the rate) of inflow after muscle injury, usually starting within the first hour and reaching a

maximum in from two to four hours. At this time of maximum constriction, the blood pressure had already fallen to a shock level, the average pressure for the series of experiments being 65 millimeters of mercury. After this, a dilation occurred which continued until death and was accompanied by a further fall of blood pressure. As already stated, the perfusion rate was still further increased after death. A curve showing the general relation between the blood pressure and peripheral response is given in Figure 4, which illustrates the averages of six experiments which were carried on over a period of four hours or more. From these results, it is apparent that the low pressure initiated by muscle injury is not primarily due to a loss of vasomotor tone or to a dilation of the blood vessels. In other words, this form of shock is not the consequence of any form of exhaustion. This conclusion is similar to that reached by Erlanger, Gesell and Gasser for shock produced by manipulation of the intestines and by occlusion of the aorta.

It might be supposed, further, that the local injury, especially when the femur is broken, would permit a sufficient amount of fat to be liberated to cause the pressure to fall. In several instances, careful examination of the lungs was made by expert pathologists, Louis B. Wilson and Henry W. Cattell; but in no instance was there evidence of any accumulation of fat. Furthermore, there was no twitching or disturbance of respiration or other sign which might indicate that fat had passed through the pulmonary capillaries into the central nervous system. The fall of pressure, therefore, cannot be attributed to fat embolism.

Although there was usually a change of respiration in the direction of greater rapidity and lessened amplitude, this was not characteristic of the period immediately after the trauma, but developed as the blood pressure fell. Commonly, the respiration became slower toward the end (Fig. 1). The absence of hyperpnea for some time after the injury, although the carbon dioxid capacity of the plasma was falling, and the later rapid and shallow breathing, which, since it was superficial, was not such as to induce a washing out of carbon dioxid from the blood, rule out acapnia as a cause of the lowered blood pressure. This conclusion was confirmed by producing shock by muscle injury, though the breathing was kept uniform by artificial means.

If the low blood pressure resulting from local trauma is not due to loss of blood into the injured region, or to reflex vasodilation, or to depression or exhaustion of the vasoconstrictor center, or to fat emboli, or to acapnia, the connection between the local damage and the general bodily state may reasonably be looked for in the remaining great connecting system—the circulation. There may be given off from the damaged tissue into the flowing blood or lymph material, which, when

carried to the rest of the body, proves toxic and disturbs the control of the walls of the vessels in such a way as to lower arterial pressure. This idea can readily be tested. The blood vessels of the leg (the iliac artery and vein) are tied and the muscles are then crushed. In the experiment recorded in Figure 5, the blood vessels of the leg were tied before the muscles were smashed, and the ligatures were left in place for thirty-three minutes after the trauma. The record shows that there was no drop of blood pressure during this period, although the arterial pressure usually begins to fall in the cat about twenty minutes after the injury. As soon as the blood flow was restored, however, the pressure promptly fell to a low level. This phenomenon can be explained

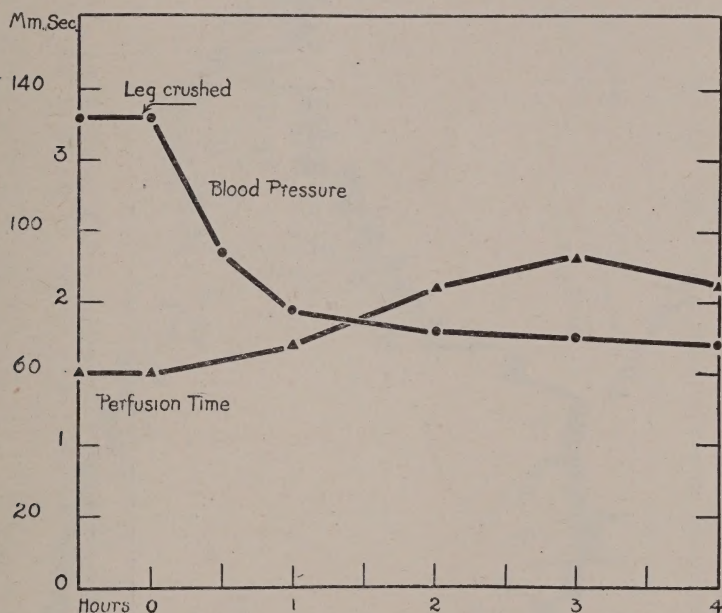


Fig. 4.—Curve plotted from the averages of six experiments showing the relationship between the perfusion rate and the blood pressure in muscle injury shock. As the blood pressure falls, there is a slowing of the perfusion rate indicating an increased tone of the arterioles.

on the supposition that when the blood is again allowed to flow a pressure-lowering substance passes, by way of the circulation, from the traumatized region to the rest of the body. The inference just set forth received support from experiments in which the muscle was injured; and, while the pressure in consequence was falling, the vessels of the leg (the iliac artery and vein) were closed. As shown in Figure 3, occlusion of the vessels may be followed by a progressive rise of pressure to the normal level. If the injury is not great, the blood pressure, after falling for a while, may spontaneously be restored. The

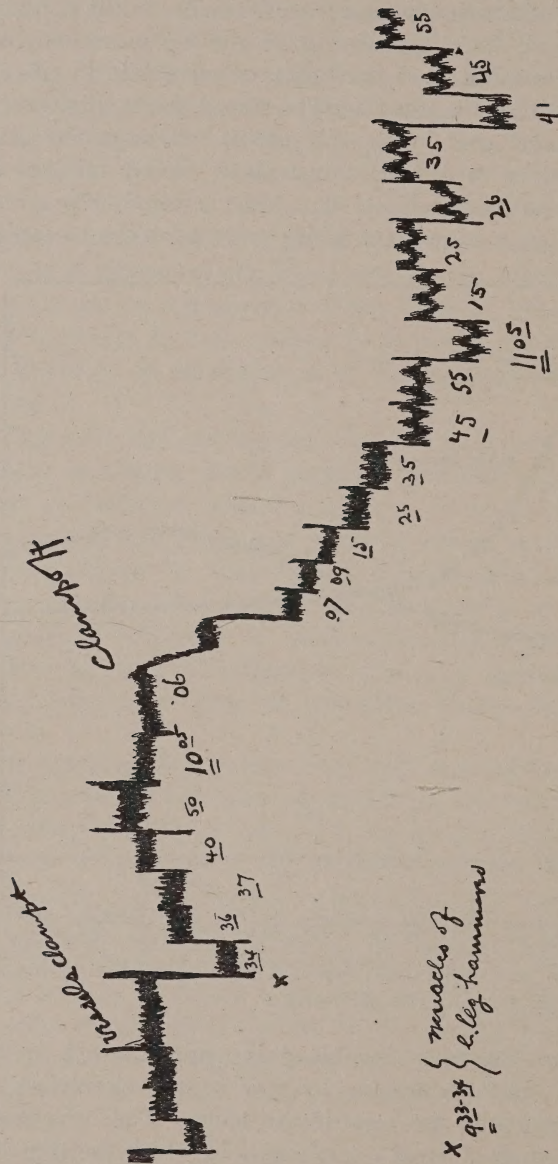


Fig. 5.—Failure of blood pressure to fall at the usual time after muscle injury (at 9:33-9:34) if the blood vessels to the injured region have been tied; on restoration of the blood flow (at 10:06), the pressure promptly falls.

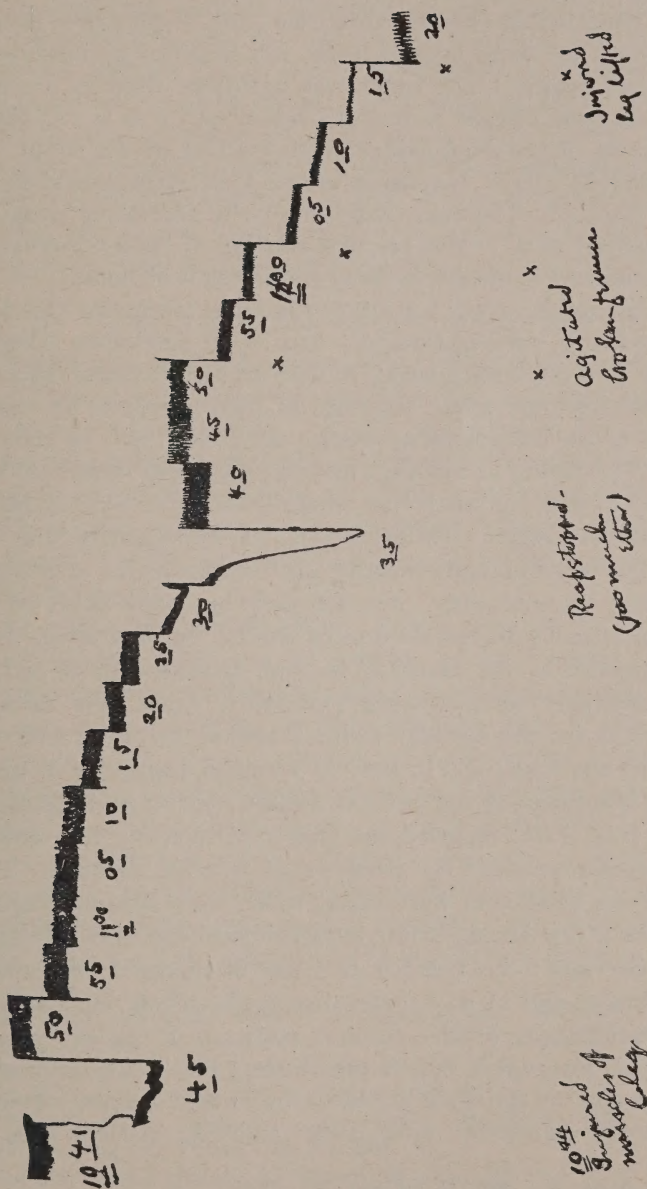


Fig. 6.—Increased rate of pressure drop after muscle injury when the ends of the broken femur were moved in the damaged tissues at x and x .

evidence indicates, therefore, that whatever may be the substance originating in the damaged tissues, it is fairly promptly changed in the body or eliminated, so that its effect is not permanent.

Further confirmation of the inference that a pressure-lowering material is given off from injured tissue was obtained by massage of the traumatized region. The result was a further drop in pressure. In Figure 6 is presented the record of blood pressure as it was falling after a smashing of the thigh muscles with fracture of the femur. At the points marked *x*, the fragments of the bone were moved in the damaged soft parts. The records taken shortly thereafter showed a greater drop than usual. The practical bearing of these observations on the importance of immobilizing bony fragments is obvious.

Other experimental work has led to the same conclusion that Bayliss and I reached in our experiments. In a recent publication, Turck¹⁹ has declared that the consequences of cell necrosis brought about in various ways affect the whole organism in such a manner as to give rise to some of the symptoms of shock. In June, 1918, he reported experiments²⁰ on injury to the thigh muscles, that were similar to those performed by Bayliss and myself in January, and referred to in March and April of that year.²¹ Unfortunately, his experiments were not accompanied by blood pressure records; and commonly, the injection of what he called "shock-toxins" was followed by rapid death of the animal rather than by the production of shock. In November, 1917, Delbet,²² impressed by the similarity between traumatic shock and the shocklike conditions accompanying peritonitis, raised the question whether intoxication did not play a rôle in certain forms of traumatic shock, whether shock was not, in fact, the result of absorption of toxins arising from disorganized and bruised tissues. Delbet and Karajonopoulos,²³ in July, 1918, reported the effects of injecting into guinea-pigs and rats the products of autolysis of crushed muscles. They found that these substances were highly toxic, sometimes making animals comatose a few seconds after intraperitoneal injection. Respiration was accelerated; the reaction to noise disappeared; the animal became immobile, and in a variable time died—effects attributed by Delbet to disturbances of the nervous system. These experiments revealed a toxic material in muscle autolysates; but it did not produce detailed analogies to the state of shock in human beings. Delbet's view that toxic substances arise from autolytic disintegration of

19. Turck: *Med. Rec.* **95**:472 (March 22) 1919.

20. Turck: *Med. Rec.* **93**:927 (June 1) 1918.

21. Bayliss, W. M.: *J. Physiol.* **52**:17, 1918. Cannon, W. B.: *Med. Bull., Med. Research Soc., Am. Red Cross*, Paris, April, 1918, p. 426.

22. Delbet: *Bull. et mém. Soc. de chir.* **43**:2121, 1917.

23. Delbet, P., and Karajonopoulos: *Bull. Acad. de méd.* **80**:14 (July 2) 1918.

muscles was questioned by Vallée and Bazy,²⁴ who noted that autolytic ferments of muscles are slow in action. They expressed doubt whether autolysis would result in a toxin sufficiently abundant or active to induce shock, and suggested that bacteria and possibly leukocytes might induce proteolytic changes capable of hastening the production of poisonous material.²⁵ It seems unnecessary to assume that tissue disintegration should be carried far in order to evoke, when injected, a fall of blood pressure. As long ago as 1903, Vincent and Sheen²⁶ proved that watery extracts of a variety of tissues, when injected into the blood stream would cause a drop of arterial tension, and Perret,²⁷ in 1909, proved that fluid pressed from raw meat ("myoserum") was highly toxic when injected intravenously.

AN EXPLANATION OF TRAUMATIC TOXEMIA

Explanation of the shock-producing effect of substances which may arise from injured tissue has its beginnings in classic experiments in the history of physiology. Nearly thirty years ago Heidenhain²⁸ demonstrated that the injection of "peptone" into the circulation would cause an increased production of lymph, persistent low blood pressure and a notable concentration of the blood. These are changes which Starling,²⁹ in 1894, attributed to increased capillary permeability, especially in the liver.

In 1919, Dale and Laidlaw³⁰ called attention to a reduction of blood pressure which can be induced by the injection of extremely minute amounts (1 or 2 mg. per kilogram in the anesthetized animal) of histamin, a substance derived from the amino-acid histidin by removal of carbon dioxid. Later, attention was called to the shocklike character of the changes which histamin occasions.³¹ The arteries are constricted (the early constriction of arteries in shock may be due, in part, to the action of toxic substances), there is oligemia, a reversed ratio of corpuscles to plasma, and failure of the cardiac output.³² If the chest is opened, the heart is seen beating regularly; but its chambers contain little blood.³³ The arteries and veins likewise contain little blood.

24. Vallée and Bazy: *Bull. et mém. Soc. de chir.* **44**:707, 1918.

25. Vallée and Bazy: *Bull. et mém. Soc. de chir.* **44**:708, 1918.

26. Vincent and Sheen: *J. Physiol.* **29**:254, 1903.

27. Perret: *Trav. du lab. de Richet* **6**:91, 1909.

28. Heidenhain: *Arch. d. f. ges. Physiol.* **49**:252-254, 1891.

29. Starling: *J. Physiol.* **17**:39, 1894.

30. Dale and Laidlaw: *J. Physiol.* **61**:318, 1910.

31. Dale and Laidlaw: *Memorandum Upon Surgical Shock and Some Allied Conditions*, English Medical Research Committee, February, 1917.

32. Dale, Laidlaw and Richards: *Traumatic Toxemia*, English Medical Research Committee, Report Series No. 26, March, 1919, p. 9.

33. Dale, Laidlaw and Richards: *Traumatic Toxemia*, p. 10.

Moreover, by the use of vital red, Dale³⁴ demonstrated that a considerable part of the blood passes out of currency. It appears, therefore, that since the blood is not in arteries and veins, it must be concentrated in capillary areas. Dale reports that the bowel shows a diffuse dusky congestion and that the smallest venules are rendered visible on its surface by their content of dark blood—a condition similar to that observed by Erlanger and his collaborators¹⁴ in the various forms of shock which they produced. By direct microscopic examination after the injection of histamin, Hooker³⁵ and also Rich³⁶ have shown that a large number of capillaries, previously not seen, become clearly defined because dilated and filled with blood. Dale and Richards³⁷ have further analyzed the action of histamin. The low pressure resulting from it is not due to relaxation of the arterioles. It is apparently due to a series of changes in which dilation of the capillaries and pooling of blood within them, poisoning of their endothelial walls so that they are abnormally permeable, escape of plasma through these walls into the tissue spaces, and consequent concentration of the corpuscles³⁸ are the main features. This thickening of the blood would accentuate the tendency for it to gather in the small vessels.

The great significance of these observations by Dale, Laidlaw and Richards is that the action of histamin may reasonably be regarded as typifying the action of a large class of poisonous protein derivatives—products of partial digestion, of bacterial action, and of tissue extraction. In 1909, Popielski³⁹ called attention to the depressor action of organ extracts and showed that “vasodilators” could be extracted from practically all tissues. In 1911, Barger and Dale⁴⁰ proved that histamin was present in the mucosa of the small intestine, in Popielski’s “vasodilators,” and also in commercial peptone. Recently, Abel and Kubota⁴¹ have adduced evidence that histamin is a widely distributed constituent of animal tissues, organ extracts and enzymatic products, whether derived from animal or vegetable proteins. In all probability, histamin is not the only constituent of tissue extracts and tissue digests capable of lowering blood pressure. Hanke and Koessler,⁴² for example, have shown that typical peptone shock can be produced by injecting peptone from which histamin is absent. We may follow Dale, therefore, in

34. Dale, Laidlaw and Richards: Traumatic Toxemia, p. 11.

35. Hooker, D. R.: Am. J. Physiol. **54**:49 (Nov.) 1920.

36. Rich: J. Exper. Med. **33**:287 (Feb.) 1921.

37. Dale and Richards: J. Physiol. **52**:144, 1918-1919.

38. Dale, Laidlaw and Richards: Traumatic Toxemia, p. 12.

39. Popielski: Arch. f. d. ges. Physiol. **128**:191, 1909.

40. Barger and Dale: J. Physiol. **41**:499, 1911.

41. Abel, J. J., and Kubota, S.: J. Pharm. & Exper. Therap. **12**:297 (June) 1919.

42. Hanke, M. T., and Koessler, K. K.: J. Biol. Chem. **43**:567 (Sept.) 1920.

regarding histamin as a type of the toxic substances derived from protein material. Although proof is still lacking that a substance, like histamin in character, is actually given off into the blood stream when the tissues are severely damaged, the effects of local tissue injury (influencing the rest of the body solely through the circulation) and the effects induced by histamin are so similar that the supposition has a high degree of probability. In both conditions, there is a fall of blood pressure. In both, there is a reduction of blood volume. In both, there is, at least in the early stages, a concentration of the blood (Fig. 1). In both, slight hemorrhage results in markedly increasing the shocklike effect. It is a matter of considerable interest that proteolytic bacteria, such as those producing gas gangrene, induce, in muscles, chemical changes, which, according to Zunz,⁴³ are accompanied by the production of histamin. Extracts of such muscles are highly toxic and rapidly depress the circulation.⁴⁴ The association of "shock" with gas infection can thus be accounted for.

The view that secondary shock is due to action of toxins arising in injured tissue places it, as Dale⁴⁵ has pointed out, in the same general category with anaphylactic shock, for that likewise is probably the consequence of poisoning by protein cleavage products. The shock-like condition produced by toxic substances arising from intestinal obstruction which Whipple and his collaborators⁴⁶ have done so much to elucidate, becomes also closely related to traumatic shock, for chemical study led them to the conclusion that the poisonous agent developed in a closed intestinal loop belongs to the primary proteoses. It is conceivable, furthermore, that the results of methods used by other investigators to produce shock, such as pinching the intestine, as employed by Githins, Kleiner, Meyer and Meltzer,⁴⁷ or interfering with the circulation, as practiced by Janeway and Ewing⁴⁸ and by Erlanger and his group,⁴⁹ may be accounted for on the basis of a toxin production. Bayliss and I¹⁸ found that after the blood flow had been wholly shut out from the hind limbs for an hour, restoration of the circulation resulted in a sharp fall of blood pressure. And Dale³² proved that if the blood vessels of the fore limb are rendered sensitive to the action of histamin by denervation, letting the blood flow through the hind

43. Zunz: *Compt. rend. Soc. de biol.* **82**:1079, 1919.

44. Report of the Shock Committee, English Medical Research Committee, Report Series No. 25, October, 1918, p. 265.

45. Dale: *Proc. Roy. Soc., B* **91**:133, 1920.

46. Whipple et al.: *J. Exper. M.* **17**:286, 307, 1913; *Ibid.* **19**:144, 166, 1914; *Ibid.* **23**:123, 1916.

47. Githins, Kleiner, Meyer and Meltzer: *Proc. Soc. Exper. Biol. & Med.* **16**:3, 1918.

48. Janeway and Ewing: *Ann. Surg.* **59**:158, 1914.

49. Erlanger, J., and Gasser, H. S.: *Ann. Surg.* **19**:389 (April) 1919.

limbs after it had been shut out for some minutes is followed not only by dilation of the vessels of the hind limbs, but also, as in histamin injection, by dilation of the vessels of the sensitized fore limb as well. Since changes in the direction of death and cell disintegration are induced when the circulation is cut off from a region—changes which are accelerated by trauma—the suggestion seems reasonable that the methods mentioned above, used by other investigators to cause shock, likewise involved toxin production.

It should not be supposed that smashed muscle is the sole source of toxic material. Pinching the intestine, as stated above, will induce shock; and I have found that crushing the tips of two or three lobes of the liver may be effective also. Possibly, substances given off by extravasated blood are likewise depressive to the circulation; at least, the injection of blood just previous to its coagulation causes a sharp drop of blood pressure.

CLINICAL EVIDENCE FOR TRAUMATIC TOXEMIA

Aside from the experimental evidence which has resulted in the building up of a theory of traumatic toxemia as a cause of shock, there are also clinical observations which extended over approximately the same period as the experimental studies, and which, quite independently, led to the same conclusion. For the clinical studies which developed and gave support to the theory of toxemia as a cause of secondary wound shock, great credit should be awarded to Quénu, professor of clinical surgery in the Medical Faculty of the University of Paris. As early as 1916, having repeatedly noted in his military service the relation between the occurrence of shock and the attendant gross damage of tissue, he began to suggest to various surgeons in the French army the desirability of securing clinical data regarding the possible presence of a toxic factor in the production of traumatic shock. In December, 1917, the observations of Rouhier, one of his former interns, were reported by Quénu; and during 1918, a series of papers were presented to the Société de chirurgie in Paris by Quénu and others—Moulinier, Santy, Marquis, La Croix, Bertein and Nimier, Rouhier and Soubeyran—which brought striking confirmation of the ideas which had been expressed. Since an excellent summary of these papers has been made by Quénu,⁵⁰ it will be unnecessary to report them here in detail. For present purposes, a brief outline of the clinical evidence that secondary shock is a traumatic toxemia will suffice.

1. Secondary shock, or what the French call "shock primitif," does not appear immediately after the receipt of wounds, as a large number of observers have testified; and therefore it is not of the nature of a

50. Quénu: *Rev. de chir.* 56:204, 1918.

nervous effect. Furthermore, the state is commonly well established before infection; and therefore it is not of bacterial origin.

2. Secondary shock is characteristically observed in association with extensive damage of muscles or with multiple wounds⁵¹ scattered over the body. This contention of Quénu is supported by the studies at Béthune and by the observations of McNee, Sladden and McCartney,⁵² who described cases in which, without injury to bones or to any vital structure or organ, there was extensive laceration of muscle, accompanied by such severe shock that most of the patients died in spite of treatment. In the case of multiple wounds the large number of small areas of damage would obviously be in sum the equivalent of destruction of a considerable mass in one region. The increase of undetermined nitrogen in the urine and of total nonprotein nitrogen, as well as residual nitrogen, in the blood of shock patients⁵ may be accounted for as a consequence of the absorption of material from the traumatized area, and also, perhaps, as the effect of tissue damage done by circulating toxins.

3. Everything that favors absorption at the region of injury is favorable to the development of shock. Thus, in the observations reported by Quénu,⁵¹ the development of shock is most severe when the region of damage communicates with the exterior by only a small orifice. The negative aspect of this evidence is presented by cases in which a large fleshy mass, along with the skin which covers it, is carried away by a missile; in such instances, shock is slight or wholly absent.⁵³

4. Anything that delays or checks absorption from the injured region delays the development of shock; but if there is a sudden removal of the check, serious results follow. In support of this point, Quénu⁵⁴ cites an incident observed by Rouhier:

A man with a crushed foot was brought in with a tourniquet placed very tightly below the knee. The leg was tense, dark-colored and full of blood; but there was no sign of shock. Rouhier performed a conservative operation and then removed the tourniquet. Three hours after the operation, the patient was in a state of intense shock.

Gregoire⁵⁵ has reported the analogous case of a lieutenant caught in a dug-out after a shell burst. His left thigh was compressed between two logs. Thus, he remained for twenty-four hours, alert, guiding the efforts of those

51. Quénu: *Rev. de chir.* **56**:270, 1918.

52. McNee, Sladden and McCartney: *Observations on Wound Shock, Especially with Regard to Damage of Muscle*, English Medical Research Committee, Report Series No. 26, March, 1919, p. 35.

53. Quénu: *Rev. de chir.* **56**:271, 1918.

54. Quénu: *Rev. de chir.* **56**:272, 1918.

55. Gregoire; cited by Quénu: *Rev. de chir.* **56**:272, 1918.

who were delivering him. His general condition was good; but he was pale, with a pulse small and rapid and a slightly accelerated respiration. There was no wound; the foot, leg and knee, however, were purplish and cold; above the knee there were two deep hollows formed by the pressure of the logs. Some hours after his rescue, the officer became restless; and, although treatment for shock was undertaken, he died thirty-two hours after the pressure was removed from the leg. There was no indication of nervous depression and no bleeding in this case. The shock appeared on permitting the circulation to return to the damaged tissue.

Five cases similar to these were reported to me from various surgeons in the hospitals of the American Expeditionary Forces in France. One instance was especially striking: A tourniquet had been in place on the upper arm for an uncertain period; but the wound in the wrist was so slight that the surgeon proceeded to clean it and take off the compression. The patient was in good condition before the tourniquet was removed. A short time thereafter, however, he went into profound shock and died. It is obvious that the state developed in these human cases was quite like that developed experimentally by Janeway and Ewing, by Erlanger and his collaborators, and by Bayliss and myself, when a continued low blood pressure was induced by interference for several hours with the circulation to a considerable part of the body.

The converse of the foregoing observations is seen when after a very severe wound the region is isolated by a tourniquet and the limb is amputated proximal to, and without removing, the tourniquet. Rouhier⁵⁶ reports a case of this type in which no shock appeared either before or after the operation.

5. Suppression of the injured region, if not too long delayed, causes shock to disappear. Much evidence in support of this statement might be cited. I had occasion to note such cases at Béthune; and Quénu and Rouhier⁵⁷ have described in detail instances of the rapid disappearance of shock after cutting away traumatized tissue. McNee, Sladden and McCartney⁵² have declared that when a quick amputation of a lacerated region is possible, "the operation is commonly followed by a remarkable and maintained improvement, so rapid and striking as to appear a direct sequel to the removal of the damaged limb." And they cite the case of a wounded man who was too shocked to allow any movement whatever, and in whom a similar good result was obtained by tying a tourniquet as tightly as possible around the limb which was so badly smashed that amputation was seen to be inevitable if the patient survived. The observations of Santy⁵⁸ on the effects of

56. Rouhier, cited by Quénu: *Rev. de chir.* **56**:272, 1918.

57. Quénu and Rouhier: *Rev. de chir.* **56**:273, 1918.

58. Santy, cited by Quénu: *Rev. de chir.* **56**:233, 234, 1918.

delaying operation on the severely wounded confirm on a larger scale the foregoing individual instances. In a series of seventy-nine cases of nontransportable wounded soldiers, in which the time between the receipt of the wounds and the surgical treatment was known, the mortality was only 11 per cent. when the operation was performed in the first three hours. It rose to 37 per cent. when there was a delay of between three and six hours (though infection is not marked until after six hours), and was 75 per cent. in the eighth and ninth hours. These figures vividly illustrate what may reasonably be expected if time is given, both for the disintegration of damaged tissue and the absorption of toxic material.

The foregoing experimental and clinical testimony, most of which was gathered only in the last two years of the war, gives a quite new turn to ideas regarding the nature of shock. In this connection, the argument of Groeningen,⁵⁹ written in 1885 in support of the nervous origin of shock, is of interest. He pointed out that shock is more frequent after shell wounds and crushing accidents than after cuts and stabs; more frequent with large missiles than with rifle bullets; more frequent with amputations and resections near the trunk than distant from it; more frequent in operations which expose a large rather than a small surface, and more frequent with a prolonged operation than with a short one. All these considerations, he cited as showing that violent stimulation and shattering of nerves are the occasion for shock. It is clear, however, that they may quite as well be instanced as the conditions which are most favorable for causing the death of considerable masses or areas of tissue (thus liberating toxic agents) and for rendering the organism sensitive to the action of such agents.

In the development of our conception of the effects of extensive burns, there has been an evolution of ideas similar to that which has occurred with regard to traumatic shock. Forty years ago, Sonnenberg⁶⁰ attributed death from burns to a reflex depression of vasomotor tone. Modern studies⁶¹ have shown that there is, as in shock, a great increase in the number of erythrocytes, i. e., a concentration of the blood and an enormous mobilization of leukocytes. The suggestion of recent writers⁶² is that here too, death, when delayed, is the outcome

59. Groeningen: Ueber den Shock, Wiesbaden, 1885.

60. Sonnenberg: Deutsch. Ztschr. f. Chir. **9**:138, 1877; Virchows Arch. f. path. Anat. **80**:381, 1880.

61. Becker and Schnitz: Klinische und chemische Beiträge zur Pathologie der Verbrennung, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **31**:416, 1919. Weiskotten, H. G.: Histopathology of Superficial Burns, J. A. M. A. **72**:259 (Jan. 25) 1919.

62. Bardeen: Bull. Johns Hopkins Hosp. **9**:137, 1898. Eyff: Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **4**:428, 1901. Pfeiffer: Virchows Arch. f. path. Anat. **180**:367, 1905. Vogt: Ztschr. Exper. Path. u. Pharm. **11**:191, 1912.

of an intoxication, probably by protein derivatives set free from the area of tissue destruction. The present conception seems to be that not only the shock following burns, but also the delayed shock consequent on severe trauma, is properly placed in the same category with other forms of general depression of bodily functions and defective circulation due to the setting free of toxic material in the body.

